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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	PAPER NUMBER
1652	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,223	CHENG ET AL.	
	Examiner	Art Unit	
	IQBAL H. CHOWDHURY	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 47-56 are currently pending.

In response to a previous Office action, a final action (mailed on March 16, 2010), Applicants filed a response and Notice of Appeal on June 29, 2010, is acknowledged.

Claims 47-56 are under consideration and are present for examination.

Applicants' arguments filed on June 29, 2010, have been fully considered and are deemed persuasive to overcome all the rejections as previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

New Claim Objections

Claims 47-55 are objected to in the recitation "SEQ ID NO.", which should be "SEQ ID NO:". Appropriate correction is required.

Claims 47-55 are objected to in the recitation "a modified, full-length recombinant human arginase I ------, which is covalently linked to at least one polyethylene glycol (PEG) molecule", which should be "a modified, full-length recombinant human arginase I ------, wherein said human arginase I is modified by covalently linked to at least one polyethylene glycol (PEG) molecule". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a human rectal cancer comprising administering to a subject a pegylated recombinant human arginase I of SEQ ID NO: 9, does not reasonably provide enablement for a method for treating a human liver, breast or colon cancer by administering to a subject a pegylated recombinant human arginase I of SEQ ID NO: 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands (858 F.2d 731,737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows:

(1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The factors, which have, lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed below:

The breadth of the claims:

Claims 47-56 are so broad as to encompass a method for treating human liver, breast or colon cancer by administering to a subject a pegylated recombinant human arginase I of SEQ ID NO: 9. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of cancers including liver, breast or colon cancers, which can be treated by said pegylated recombinant human arginase I broadly

encompassed by the claims. In the instant case the disclosure is limited to a method for treating rectal cancer by using pegylated human recombinant arginase I of SEQ ID NO: 9.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art:

The liver, breast, rectal or colon cancers are very diverse in terms of organ, tissue and genetic disorders, or chemical or environmental effect and mode of cancer development, which cause said cancers are different from each other, and treating the cancers of liver, breast or colon is unpredictable, although, applicants have shown a method for treating human rectal cancer using pegylated recombinant human arginase I, which require a knowledge of and guidance with regard to each of the cancers, which are very diverse. What is predicted for a method for treating rectal cancer by pegylated recombinant human arginase I, cannot be predicted for every cancer because they are different from each other. Applicants have only shown that rectal cancer can be treated with pegylated recombinant human arginase I. Besides, Vockley et al. (Arginase II, US 6316,199 B1, issue date 11/13/2001, see IDS) teach that the increased arginase activity in solid tumors including breast, ovarian, lung, colon, testicular and prostate tumors, which suggest that arginase may not be useful for treating breast, ovarian, lung, colon, testicular and prostate tumors.

The amount of direction or guidance presented and the existence of working examples:

The specification discloses a method for treating rectal cancer by using pegylated human recombinant arginase I of SEQ ID NO: 9. However, the specification fails to provide any evidence of treating human liver, breast or colon cancer by administering to a subject a pegylated recombinant human arginase I. No correlation between pegylated arginase I and effective treatment for breast, liver or colon cancer has been presented.

The specification does not support the broad scope of the claims which encompass a method for treating human liver, breast or colon cancer by administering to a subject a pegylated recombinant human arginase I of SEQ ID NO: 9 because the specification does **not** establish that other cancers including liver, breast or colon can be treated with pegylated recombinant human arginase I and the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function (treating diverse cancers), and the high degree of unpredictability of the prior art, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Withdrawn-Claim Rejections - 35 USC § 103

The previous rejection of claims 47-56 under 35 U.S.C. 103 (a) as being obvious over Vockley et al. (Arginase II, US 6316,199 B1, issue date 11/13/2001, see IDS) and Clark et al. (WO 02/44360, publication 6/6/2002, see IDS) in view of Mehvar et al. (Modulation of the pharmacokinetics and pharmacodynamics of proteins by polyethylene glycol conjugation, J Pharm Pharmaceut Sci, 3(1):125-136, 2000, see PTO-892) and Takaku et al.(In vivo anti-tumor activity of arginine deiminase purified from Mycoplasma arginini, Int J Cancer. 1992 May 8;51(2):244-9, see IDS) is withdrawn in view of applicants persuasive arguments. Indeed,

Vockley et al. do not teach a method of treating cancer by arginase, but rather teach the increased arginase activity in solid tumors including breast, ovarian, lung, colon, testicular and prostate tumors.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47-56 are rejected under 35 U.S.C. 103 (a) as being obvious over Tepic et al. (Therapeutic composition for treatment of cancer, WO 98/06421, publication 2/19/1998, see IDS), Vockley et al. (Arginase II, US 6316,199 B1, issue date 11/13/2001, see IDS) in view of Clark et al. (WO 02/44360, publication 6/6/2002, see IDS) and Mehvar et al. (Modulation of the pharmacokinetics and pharmacodynamics of proteins by polyethylene glycol conjugation, J Pharm Pharmaceut Sci, 3(1):125-136, 2000, see PTO-892).

Tepic et al. teach a therapeutic composition and method for the treatment of cancer including leukemia by systemic deprivation of arginine by various methods including use of arginine decomposing enzyme arginase, which degrades arginine, followed by reducing the arginine level, and modified the enzyme including arginase with polyethylene glycol (PEG). Tepic et al. also teach administering the arginase in an animal subject for reducing arginine level in said subject. Tepic et al. also identified the killing window of arginine concentration for killing cancer cell, which is below 10uM for longer than 3 days that is important for the anti-cancer effect of arginine decomposing enzyme (abstract, p1, p4-5, p7, p12-13, p26-27 and claims 1-37). Tepic et al. do not teach arginase of SEQ ID NO: 9 or histidine tagged arginase of SEQ ID NO: 2 or treating a particular cancer including liver, breast, colon or rectal cancer, and increased the half-life of the pegylated arginase for 3 days (for claim 55).

Vockley et al. teach human arginase II and I, wherein said arginase I is 100% identical to arginase I of SEQ ID BNO: 9 of the instant application. Vockley et al. also teach recombinant expression of human arginase II, expression in Sf9, Cos and *E. coli* followed by purification by affinity chromatography due to the presence of HA tag (Example 3 and 4), which results substantially purified protein (see Col 11, line 55-66). Vockley et al. further teach a pharmaceutical composition comprising human arginase II and pegylated said protein by treating with polyethylene glycol (PEG) to increase the half-life of the protein in serum and reduce the antigenicity to be an effective therapeutic composition for treating cancer (see Col 14, line 47-64). The arginase II gene was found using probes based on arginase I which was shown to have considerable sequence homology, wherein said arginase I is 100% identical to SEQ ID NO: 9 of the instant application. Vockley et al. do not teach the use of arginase I for treating liver, breast,

colon, and rectal cancer, and increased the half-life of the pegylated arginase for 3 days (for claim 55).

Clark et al. teach modified arginine deiminase, an arginine degrading enzyme, which is modified with polyethylene glycol (PEG) and a method of treating cancer including sarcomas, hepatomas (a liver cancer) and melanomas (page 2, line 28-31, page 3, line 1-3). Clark et al. do not teach increased half-life of the pegylated arginase (for claim 55) for 3 days.

Mehvar et al. teach the half-life of arginase protein of 12 hrs after pegylation with polyethylene glycol and further teach that said arginase conjugate increased the survival time in mice with Taper liver tumor (page 128, left column, line 3-8).

Tepic et al. clearly teach a therapeutic composition and method for the treatment of cancer including leukemia by systemic deprivation of arginine by various methods including use of arginine decomposing enzyme arginase, which degrades arginine, followed by reducing the arginine level, and modified the enzyme including arginase with polyethylene glycol (PEG) and reducing the arginine concentration below 10 uM. Vockley et al. clearly teach arginase I, which is 100% identical to SEQ ID NO: 9 of the instant application and a method of treating various disorders with arginase II, an isoform of arginase I having identical function of degrading arginine, wherein said arginase II is modified with PEG, which increased the half life of arginase. Vockley et al. also teach HA-tagged human arginase II. Clark et al. teach using arginine degrading enzyme for treating hepatomas, a liver cancer. Mehvar et al. teach treating mice with arginase protein (without specifying if it is arginase I or arginase II) modified with PEG, which increased the half-life of the pegylated arginase in mice to 12 hrs in a treatment of Taper liver tumor.

Therefore, combining the teachings of Tepic et al. Vockley et al. Clark et al. and Mehvar et al. it would have been obvious to one of ordinary skill in the art at the time of the invention was made to replace arginase of Tepic et al. with arginase I as taught by Vockley et al. and use the method of treating cancer as taught by Tepic et al. by using arginase I of pegylated with PEG as taught by Vockley et al. for treating cancer including liver cancer as taught by Clark et al. and administering said pegylated arginase in a subject and reducing the arginine level below 10 uM for 3 days as taught by Tepic et al. and increased the half life of pegylated arginase for at least 3 days by modifying the method of Mehvar et al. to arrive the claimed invention. The addition of His tag in the arginase of Vockley et al. is obvious because Vockley et al. showed the addition of HA tag to arginase II and adding His or HA tag is well known for protein purification and widely used in the prior art. Substituting bovine arginase of Tepic et al. with human arginase I of Vockley et al. is obvious because the two enzymes have identical activity and substituting HA-tag with His-tag is also obvious because of identical function for protein purification, which is well known and widely used in the art. See KSR Int'l Co. V. Teleflex, Inc. 82 USPQ2d 1385 (2007).

One of ordinary skill in the art would have been motivated to replace bovine arginase with human arginase I in view of its identical activity to degrade arginine for use as a therapeutic means against human cancer, wherein arginase has been shown to use in treating cancer by reducing the arginine level because cancer cell requires arginine for its proliferation and reducing said arginine eliminate cancer cells. One of ordinary skill in the art would have been motivated also to use pegylated arginase to increase the half-life of the enzyme, which will eventually reduce the serum arginine level below 10 uM (normal concentration is about 100 uM) for at least

3 days in serum to increase the effectiveness of the enzyme against malignant cell in order to treat cancer, since, reduced arginine helps cancer cell to die. Vockley et al. and Mehvar et al. clearly teach the increased half life of arginase protein by pegylation, which is effective for the treatment and one ordinary skill in the art would be able to increase the half life of pegylated arginase I and subsequently decrease the arginine level below 10 uM for 3 days from the teachings of Tepic et al.

One of ordinary skill in the art would have a reasonable expectation of success because Tepic et al. could successfully used arginase for treating cancer.

Therefore, claims 47-56 would have been *prima facie* obvious to one of ordinary skill in the art.

Conclusion

Status of the claims:

Claims 47-56 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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Iqbal Chowdhury, Patent Examiner
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